Supplement S3 - Part A: Additional Files Automatically Produced by NONMEM (intro7, [1]):

Additional files are in row, column format, with user controlled number format, allowing any delimiter, and any number of significant digits displayed. Examples of these additional output files are available in Supplemental Material S1 for problem 402, and Supplemental Material S2 for problem 504.

root.ext: A raw output file will be produced that provide numerical results in a columnar format. The raw output file name is by default *root*.ext, where *root* is the root name of the control stream file. Or, the name is provided by the user using a FILE= parameter added to the $EST record. A raw output file has the following format:

A header line that begins with the word Table, such as:

```
TABLE NO.      1: First Order Conditional Estimation with Interaction: Goal Function=MINIMUM
VALUE OF OBJECTIVE FUNCTION
```

This header line provides the analysis text (same as given on the #METH: line in the main report file), followed by the goal function text (same as given on the #OBJT: line in the report file).

The next line contains the column headers to the table, such as (this is actually all on one line in the file):

```
ITERATION     THETA1       THETA2       THETA3       THETA4        SIGMA(1,1)    OMEGA(1,1)
OMEGA(2,1)    OMEGA(2,2)   OMEGA(3,1)   OMEGA(3,2)   OMEGA(3,3)    OMEGA(4,1)    OMEGA(4,2)
OMEGA(4,3)    OMEGA(4,4)   OBJ
```

This is followed by a series of lines containing the intermediate results from each printed iteration (six significant digits), based on the PRINT= option setting:

```
          10   1.00131E+01   3.90079E+00   7.06085E+01   8.99525E+00   1.13865E-02   1.87885E-02
0.00000E+00   3.15197E-02   0.00000E+00   0.00000E+00   1.15694E+00   0.00000E+00   0.00000E+00
0.00000E+00   2.39182E-02   290.456900129605
```

For the above example, each of the values, up to the next to last one, occupies 13 characters, including the delimiter (in this example the delimiter is a space). The last value is the objective function, which occupies 30 characters, to allow for the largest range of objective function values, and the greatest expression of precision.

The iteration number, which is the first value in every line, is typically positive, but also may be negative under the following conditions:

1) The burn-in iterations of the MCMC Bayesian analysis are given negative values, starting at –NBURN, the number of burn-in iterations requested by the user. These are followed by positive iterations of the stationary phase. A Bayes example is given in the advanced tutorial.

2) The stochastic iterations of the SAEM analysis are given negative values. These are followed by positive iterations of the accumulation phase. An SAEM example is shown in the advanced tutorial.

3) Iteration -1000000000 (negative one billion) indicates that this line contains the final result (thetas, omegas, and sigmas, and objective function) of the particular analysis. For BAYES analysis, this is the mean of the non-negative iterations (stationary samples) listed before it.

4) Iteration -1000000001 indicates that this line contains the standard errors of the final population parameters. For BAYES, it is the sample standard deviation of the stationary samples.

5) Iteration -1000000002 indicates that this line contains the eigenvalues of the correlation matrix of the variances of the final parameters (if requested with $COV … PRINT=E).

6) Iteration -1000000003 indicates that this line contains the condition number , the lowest, and the highest, eigenvalues of the correlation matrix of the variances of the final parameters, respectively (if requested with $COV … PRINT=E).

7) Iteration -1000000004 indicates this line contains the OMEGA and SIGMA elements in standard deviation/correlation format.

8) Iteration -1000000005 indicates this line contains the standard errors to the OMEGA and SIGMA elements in standard deviation/correlation format

9) Iteration -1000000006 indicates 1 if parameter was fixed in estimation, 0 otherwise.

10) Iteration -1000000007 lists termination status (first item) followed by termination codes.

11) Iteration -1000000008 lists the partial derivative of the log likelihood (-1/2 OFV) with respect to each estimated parameter. This may be useful for using tests like the Lagrange multiplier (or score) test, when used in combination with the variance of the estimates.

12) Additional special iteration number lines may be added in future versions of NONMEM.

The raw output file is provided automatically, independent of the formatted files that may be requested by the user using the $TABLE command.

Some additional auxiliary files also automatically outputted by NONMEM are:

root.cov: Full variance-covariance error matrix to thetas, sigmas, and omegas

root.cor: Fully informative correlation matrix of estimates, with standard errors as diagonal elements, and correlation values on the off-diagonal elements.

root.coi: Inverse covariance matrix (Fisher information matrix) to thetas, sigmas, and omegas

root.phi: Individual etas (eta()), their variances (etc()), and individual objective function values.

A complete list of auxiliary files is given in ([1], intro7).

Supplement S3 - Part B: A Guide to the NONMEM User's Guides

A brief description of the The NONMEM User's Guides is given here, and are listed in the order of recommended reading:

Guide V: Introduction to NONMEM. This guide covers the basic ideas of nonlinear mixed effects modeling

Guide VI: PREDPP Guide. This guide offers the details of each of the internal models of PREDPP. Some ADVANs are specific, while others are very general: The list of ADVANs is listed in Table 1.

Guide VIII: Help Guide. This guide is a language reference guide to all of the options that are available in NONMEM. Some of the options have complicated actions and their use may be further described in the following guides:

Intro7: Introduction to NONMEM 7. This guide describes in detail how one may use the advanced estimation methods such as IMP, SAEM, ITS, and BAYES. Also, it describes all changes that have occurred since NONMEM VI, from NONMEM 7.1 to the present version of NONMEM 7.4.

Guide IV: NM-TRAN Guide. This guide has some additional information of how the front end control stream reader program NM-TRAN can be further used to control your analysis.

Guide III: NONMEM 7.3 Installation Guide. Along with the readme_74 document, this guide offers detailed information on installing NONMEM on Windows, Macintosh, or Linux, and how to install for parallelization on multi-core single computers and computer clusters.

Nonmem_reserved_variables: This is a text file in the ..\util directory, which contains descriptions and source definitions of reserved NONMEM variables that may be of use to the user.

The following guides are for the reader who is interested in delving deeper into the methods used in NONMEM.

Guide II: Users Supplemental Guide. Detailed derivations and descriptions of the basis of first order (FO) nonlinear mixed effects modeling. Although FO is no longer used as the main analysis method, this guide offers a good mathematical grounding of nonlinear mixed effects modeling, and of the construction of the OMEGA and SIGMA variances structures, including how eta correlations and epsilon correlations are dealt with by NONMEM.

Guide VII: A mathematical description of the FOCE and Laplace methods

NONMEM7_Technical_Guide: Detailed mathematical derivations and descriptions of the Monte Carlo and expectation-maximization methods in NONMEM.

The remaining guides are of historical interest:

Guide I. Users Basic Guide. This guide was appropriate for NONMEM versions I and II, before NM-TRAN was introduced as the user interface in NONMEM version III.

Supp: NONMEM V Supplemental Guide. This guide served to list the changes from NONMEM IV to V at the time of V's release. Guide VIII is now used for a reference to all options in the present version.

Intro: Introduction to Version VI. This guide served to list the changes from NONMEM V to IV at the time of VI's release. Guide VIII is now used for a reference to all options in the present version.